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EXAMINER
SPECTOR,L

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DATE MAILED: 08/09/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/17/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 30-35, 38-43 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-29, 36, 37 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 30-35, 38-43 are rejected.
5. ☒ Claims 39-43 are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to make an enabling disclosure.

The disclosed utilities of the method in regards to in vivo treatment and/or prevention of HIV infection (e.g. page 21§3-4, page 22§1 et seq., page 29§1-2) are not believable in view of contemporary knowledge of the art. Under 35 U.S.C. 132, Applicant is required to either (1) submit appropriate proofs in compliance with 35 U.S.C. 101 and 112 to substantiate this alleged utility; or (2) cancel all disclosure of the in vivo anti-HIV utility from the specification. The current specification provides enablement only of the production of the peptides of the invention and their use in vitro. No evidence of in vivo utility is presented, nor has the applicability of the in vitro test results to the use of the claimed protein in vivo been established. M.P.E.P. 608.01(p); In re Gotleib, 140 USPQ 665. See also M.P.E.P. 1302.01 concerning correspondence between specification and claims.

Claims 31 and 39 are rejected under 35 U.S.C. § 101 for the reasons cited above.

Enablement of the current specification as filed is not commensurate in scope with claims to CD4-Ig chimeric proteins linked to toxins of any sort. Specifically, although the ordinary artisan would know how to make such toxin conjugates, the only demonstrated method of using the instant peptides is as diagnostic reagents, and toxin conjugates are not generally considered

to be useful diagnostic reagents.

The deposit of biological organisms is not considered by the Examiner to be necessary for enablement of the invention as claimed (see MPEP 608.01(p), part C). Examiner acknowledges the deposit of organisms under accession numbers ATCC 40949-52, and 75192-4 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in the event that the claims are amended such as to necessitate a biological deposit, applicants would be required to state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in order to be fully compliant with the requirement.

Claims 31-33, and 39-41 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 32, 33, 36, 37 and 39-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36 and 37 are indefinite and incomplete; it is not clear how many of the specified comprise the heterotetramer, nor what the other components of the heterotetramer are.

Claims 32, 33, 40 and 41 are incomplete for failing to recite the more than a single agent as comprising the composition. The Examiner notes that a fused CD4-Ig molecule which is further linked to a toxin is still only a single agent, albeit more complex in nature. The Examiner suggests amendment of the preamble of such claims to delete reference to a composition, or alternatively, amendment of the claim to recite additional agents.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 30-43 are rejected under 35 U.S.C. §103 as obvious over U.S. Patent Number 5,116,964 either alone or taken with applicants admissions in the specification of the state of the prior art.

The '964 patent relates to immunoglobulin fusion proteins which comprise immunoglobulin constant regions fused to "ligand binding partners", which may include the CD4 binding region (see column 5). Column 5, lines 55-60 state that the fusions of the invention may be further modified by linkage through peptidyl or in vitro generated bonds to additional moieties such as toxins, labels or other groups. Embodiments include hetero- or homo-multimers, particularly dimers and tetramers (col. 10). Suitable immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2, -3, or -4, IgA, IgE, IgD or IgM (bottom of column 14). The preferred embodiments specified at the first paragraph of column 15 include either the entire heavy chain constant region of the immunoglobulin, or "a sequence beginning in the hinge region just upstream of the papain cleavage site..."; the Examiner notes that both these preferred embodiments preserve the disulfide bond region of the hinge region, as specified in the current specification at page 10. The '964 patent states that the polypeptides of the invention therein are useful as cell surface adhesion molecules and ligands, and are useful in therapeutic or diagnostic compositions and methods.

The particular peptides claimed in the current application are not specifically disclosed in the '964 patent. However, one having ordinary skill in the art would find it obvious to follow the teachings and motivations therein to construct the claimed CD4-Ig conjugates. One of ordinary skill in the art would further have found it obvious to attach the chimeric protein to toxins or labels as further suggested by the '964 patent in order to use the chimeric protein as a cytotoxic or diagnostic reagent, respectively, in view of the art-recognized utility of such reagents as evidenced by the '964 patent.

In the specification, applicants make the following admissions of record: At page 8, applicants admit that the prior art recognized that anti-HIV antibodies were capable of enhancing infection of monocyte/macrophage cells, presumably by cross-bridging HIV and Fc receptors, and further admit that the prior art was aware that two of the three known Fc receptors have no affinity for IgG2, and the third (FcRII) has only low affinity for IgG2. Given that these facts were known in the prior art, it would have been obvious to the ordinary artisan at the time the invention was made that when constructing CD4-Ig fusions as suggested by the '964 patent, to fuse the CD4 binding domain to IgG2 to lessen the potential for enhancing, rather than inhibiting infectivity of the virus.

Claims 30-43 are rejected under 35 U.S.C. § 103 as being unpatentable over WO89/02922 in view of Capon et al. (Nature).

WO89/02922 discloses CD4-Immunoglobulin adhesons, which comprise the gp120-binding domain of CD4 fused to various immunoglobulin constant regions. The paragraph on p. 10 states "It is preferable that the V1V2 or V1-4 (of CD4) be fused at their C-termini to the immunoglobulin constant region. The precise site at which the fusion is made is not critical..." At the top of the next page, particular species comprising the first 180 amino acids of CD4 are disclosed, linked to the kappa or IgG1 heavy chain constant region. The paragraph bridging pp. 11-12 states, "According to this invention, CD4-IgG immunoadheson chimeras are readily secreted wherein the CD4 epitope is present in heavy chain dimers, light chain monomers or

dimers, and heavy and light chain heterotetramers..." The first paragraph, p. 13 states suitable fusion partners to include IgG-1, -2, -3 or -4, IgA, IgE, IgD, or IgM. The paragraph bridging pp. 15-16 discloses fusions which further comprise an adheson conjugated with a toxin. Pharmaceutical compositions are disclosed at p.27,§1. The WO publication does not specifically disclose tripartite chimeras combining CD4, Ig and toxin or marker moieties.

Capon et al., in their article on designing CD4 immunoadhesons for AIDS therapy, disclose that one can increase the stability of a rapidly cleared molecule (eg. CD4) by fusing it to a long lived molecule, such as an immunoglobulin, or the Fc fragment thereof (see p. 527).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to construct a chimeric protein comprising CD4 and a toxin or marker as disclosed by the WO publication, and further comprising an immunoglobulin constant region in view of the teaching by Capon et al. that such would be expected to increase the half-life of the chimeric molecule, because of the art-recognized utility of generating a more stable species. One of ordinary skill in the art would further have found it obvious to attach the chimeric protein to toxins or labels as further suggested by the WO publication in order to use the chimeric protein as a cytotoxic or diagnostic reagent, respectively, in view of the art-recognized utility of such reagents as evidenced by the WO publication.

No claims are allowed.

Any inquiry concerning this communication should be directed to Lorraine Spector, Ph.D. at telephone number (703) 308-0196.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

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